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DRUG SAFETY

Teicoplanin anaphylaxis associated with surgical prophylaxis

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AIMS

The aim of this paper is to determine the rate of true anaphylaxis to teicoplanin.

METHODS

A case-series including all suspected anaphylactic reactions attributed to teicoplanin anaphylaxis within a single institution over a 29-month period were categorised according to the probability of true IgE-mediated anaphylaxis using previously published criteria. The number of patients who received teicoplanin was determined and used to calculate the rate of IgE-mediated anaphylaxis.

RESULTS

Approximately 18 800–19 600 patients received teicoplanin during the study period, during which there were 14 cases of suspected anaphylaxis attributed to the administration of teicoplanin: five were categorised as definite IgE-mediated anaphylaxis, four as probable, two as uncertain and three were excluded. Of the excluded cases, two were found to have positive intradermal skin testing to alternative agents (rocuronium and chlorhexidine), and one did not meet the published clinical criteria.
We therefore calculated the rate of IgE-mediated anaphylaxis to be between 0.046% and 0.059% (equating to between 1:2088 and 1:1655).

CONCLUSIONS

This is the first study to calculate a rate of IgE-mediated anaphylaxis to teicoplanin in clinical practice. Our case series suggests that these life-threatening reactions occur less commonly than reported by the manufacturers. Mast cell tryptase is unreliable when used to predict the likelihood of IgE-mediated anaphylaxis to teicoplanin.

Introduction

Teicoplanin is a lipoglycopeptide antimicrobial commonly used to treat and prevent Gram-positive infections, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. To improve antimicrobial stewardship, many organisations have moved from cephalosporins to teicoplanin for surgical prophylaxis. The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) 2016 report has demonstrated a steady increase in the use of teicoplanin between 2010 and 2015 [2].

As part of a strategy to reduce the number of cases of *Clostridium difficile* infection at the Royal National Orthopaedic Hospital (RNOH), in September 2013 the local antimicrobial regimen for standard orthopaedic prophylaxis changed from, starting at induction, cefuroxime 1.5 g continuing every 8 h

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for three doses, to single doses of teicoplanin (10 mg kg^{-1} rounded to the nearest 200 mg to use full vials) plus **gentamicin** (5 mg kg^{-1}). Subsequently, there were concerns of suspected anaphylactic reactions to teicoplanin occurring in theatres. Initially it was unclear whether these were anaphylaxis or due to rate-related infusion reactions, which are known to occur with other glycopeptide-related antimicrobials [3]. As a precaution, in October 2014, the Drugs and Therapeutics Committee (DTC) advised all staff administering teicoplanin to dilute the drug in 100 ml of 0.9% sodium chloride and infuse over 30 min instead of the manufacturer's recommendation of slow bolus injection.

The rate of confirmed IgE-mediated anaphylaxis to teicoplanin is currently unknown. A recently published National Audit Project aimed to identify individual experiences and perceptions of UK anaesthetists' experiences with severe perioperative anaphylaxis. Out of the 11 000 respondents, teicoplanin was the suspected trigger in 28% of cases of antibiotic-related anaphylaxis, second only to penicillins. This was despite only 5% of respondents perceiving it to be high risk for anaphylaxis. The survey did not aim to establish the incidence of anaphylaxis to any agent, but did conclude that perioperative anaphylaxis was largely under-reported [4]. The manufacturer's pre- and post-marketing surveillance reports the frequency of anaphylaxis to be between 0.1% and 1%; higher than for other antimicrobials [5]. However, surveillance suggests suspected anaphylaxis which is not confirmed by skin-prick testing (SPT) or serum mast-cell tryptase levels (MCT). Only case reports of true IgE-mediated anaphylaxis are published. It is not possible to calculate how common these events are, as the total number of exposed patients is unknown [6]. The currently available information suggests that anaphylaxis to teicoplanin exists, may be higher than for other antimicrobials, and is not currently perceived to be high risk by many UK anaesthetists.

The aim of our study is to determine the rate of IgE-mediated anaphylaxis to teicoplanin in our institution.

Methods

In October 2013, the DTC implemented a protocol to monitor and refer all suspected cases for allergy investigations in accordance with national guidelines [7]. Bulletins were issued to all clinical staff requiring them to report suspected anaphylactic reactions to our consultant microbiologists and electronically through the organisation's incident reporting system. The Research and Development (R&D) department at the RNOH reviewed the study and concluded that it fits into the category of service evaluation and as such does not require approval from Research Ethics Committee (REC) or the R&D Office.

To calculate the rate of teicoplanin anaphylaxis, we established the number of cases of IgE-mediated anaphylaxis to teicoplanin (numerator) and divided this by the number of patients who received teicoplanin during the study period (denominator).

For the numerator, we conducted an analysis of the allergy test results undertaken on all suspected cases of anaphylaxis to teicoplanin over a 29-month period (1 October 2013–31 March 2016). We classified the likelihood of each reaction being due to anaphylaxis to teicoplanin as definite, probable, uncertain, or excluded using published criteria set out in a recent case series by Savic *et al*. [6] (see Table 1). The probable and definite cases were used for the lower end of the range, and the uncertain cases were included for the higher end.

At the RNOH, teicoplanin is prescribed but not dispensed individually for patients, and is available as a stock medicine in theatres where anaesthetists prepare each dose on a case-by-case basis. The denominator was calculated by two methods using pharmacy issue data and the results of local surgical antimicrobial prophylaxis audits, conducted regularly during the study period. The first method was to divide the total amount of teicoplanin issued to theatres by the average dose of teicoplanin prescribed from audit data. A second method of calculating the denominator was used to validate this by multiplying the total number of surgical procedures performed during the study period, by the proportion of all surgical procedures that received prophylactic teicoplanin from audit data. Both estimates where used to calculate the upper and lower limits of the range for the denominator.

To calculate the rate of IgE-mediated anaphylaxis to teicoplanin, the upper and lower end of the ranges for the denominator and the numerator were used.

To establish whether advising all staff administering teicoplanin to dilute the drug in 100 ml of 0.9% sodium chloride and infuse over 30 min had any effect on the number of suspected cases of anaphylaxis, we used the same method above to calculate the rate of IgE-mediated anaphylaxis in the 12 months before and the 12 months after issuing the recommendation.

Table 1

Criteria to define likelihood of allergic anaphylaxis, and grading of the certainty of diagnosis based on these criteria. Adapted from Savic *et al*. [6]

	Criteria defining the likelihood of allergic anaphylaxis	Grading of the certainty of diagnosis of allergic anaphylaxis
1	Reaction within 15 min of administration of Teicoplanin	**Definite:** Met all criteria
2	≥ 2 Features of anaphylaxis present	**Probable:** Met criteria 1, 2 & 5, plus 3 or 4
3	Positive skin testing or challenge testing	**Uncertain:** Met criteria 1, 2&5
4	Raised serum mast cell tryptase	**Excluded:** Any others
5	Alternative diagnosis excluded	

Nomenclature of ligands

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [8].

Results

During the study period, 14 suspected cases of teicoplanin anaphylaxis were reported by the attending anaesthetists. All were referred for further investigation at a specialist allergy testing centre. Patient characteristics, and planned procedure are shown in Table 2.

Table 3 outlines the clinical features present at the time of the event as described in the attending anaesthetist's incident report and medical records. All but one case had at least two clinical signs of anaphylaxis.

Table 4 shows the administration characteristics, including whether the patient had previously received teicoplanin, the dose received, the mode of administration and other drugs that were coadministered.

Determining the likelihood of IgE-mediated teicoplanin anaphylaxis

The allergy investigation results are shown in Table 5 together with the likelihood of IgE-mediated anaphylaxis. Of the 14 patients, five where categorised as definite, four as probable, two as uncertain and three were excluded. Of the three excluded cases, two were found to have positive intradermal skin testing to alternative agents, **rocuronium** and chlorhexidine, and one did not meet the published clinical criteria proposed by Savic *et al*. [6].

Of the five cases of definite anaphylaxis, all but one fully met the criteria. Patient 11, had an immediate severe reaction following teicoplanin administration but did not have MCT measurements taken at the time of the reaction, and hence could not be fully classified. Intradermal skin tests were later found to be positive for teicoplanin, and negative for coadministered agents (**fentanyl**, rocuronium and **propofol**). A similar case described by Savic *et al*. was classified as definite, based on the strong clinical evidence of anaphylaxis to teicoplanin [6].

All the four patients classed as probable anaphylaxis fulfilled the published criteria. Two had an immediate severe reaction following teicoplanin administration, but without an MCT rise above the reference range. However, intradermal skin tests were later found to be positive for teicoplanin, and negative for coadministered agents (Patients 2 and 7). Patients 3 and 9 both had immediate severe reactions following teicoplanin administration, with an MCT rise above the reference range. Both these patients were later found to have negative skin testing to teicoplanin, as well as all other coadministered agents.

Both patients classified as uncertain had an immediate severe reaction following teicoplanin administration, but neither an MCT rise above the reference range nor positive skin allergy testing.

Of the three excluded patients, two had an immediate severe reaction following teicoplanin administration but were subsequently found to have positive skin testing to coadministered agents (Patient 5 to rocuronium and Patient 12 to chlorhexidine). Finally, Patient 10 developed a widespread urticarial rash later than 15 min following teicoplanin

Table 2

Patient characteristics and planned procedure for patients with suspected teicoplanin anaphylaxis

Case number	Age	Gender	Planned procedure	Date of procedure	Outcome
1	69	Male	Resection of a cervical tumour	20/11/2013	Survived
2	43	Female	Right total hip replacement	15/01/2014	Survived
3	28	Female	Excision of a non-giant cell tumour on the right proximal fibula	14/01/2014	Survived
4	36	Male	Removal of spinal metalwork	25/04/2014	Survived
5	61	Female	Right total shoulder replacement	17/07/2014	Survived
6	37	Female	Second stage revision of a total shoulder replacement	24/07/2014	Survived
7	16	Female	Left medial patellofemoral ligament reconstruction	27/08/2014	Survived
8	63	Male	Incision and drainage of a left patellar tendon graft infection	12/09/2014	Survived
9	52	Female	Revision of a spinal of metalwork	17/11/2014	Survived
10	13	Female	Ulna osteotomy	06/03/2015	Survived
11	60	Female	Wound debridement following excision of a spinal tumor	24/03/2015	Survived
12	71	Female	Revision of a total shoulder replacement	09/07/2015	Survived
13	16	Female	Removal of spinal metalwork	09/09/2015	Survived
14	64	Male	Second stage revision of a total hip replacement	16/10/2015	Survived

Table 3

Clinical features present at the time of suspected teicoplanin anaphylaxis

Case number	Urticaria/ Angioedema	Hypotension	Tachycardia	PEA arrest	Bronchospasm	Hypoxaemia
1	✓	✓	✓	✓	-	-
2	✓	✓		-	-	-
3	-	✓	✓	✓	✓	-
4	-	✓	✓	-	-	✓
5	-	✓	✓	-	✓	-
6	✓	✓	✓	-	-	-
7	✓	✓	-	-	-	-
8	✓	✓	✓	✓	-	-
9	✓	✓	-	-	-	-
10	✓	-	-	-	-	-
11	-	✓	✓	-	-	-
12	✓	✓	✓	-	-	✓
13	-	✓	✓	-	✓	-
14	✓	✓	✓	-	-	-

administration, with no bronchospasm or cardiovascular compromise. In the absence of allergy investigation results, teicoplanin anaphylaxis was excluded based on a clinical history inconsistent with IgE-mediated anaphylaxis.

Establishing the number of patients who received teicoplanin

In total, 23 636 surgical procedures were performed at the RNOH during the 29-month study period. Of these, 47.0% were on females and 53.0% on males. The average age was 45.9 years (range 0–99).

Our audit data showed that 77% of all surgical procedures involve the administration of teicoplanin at an average dose of 528 mg (range 200–1000 mg) per patient. Using these results, we calculate that out of the 23 636 surgical procedures conducted at the RNOH during the study period, 18 200 patients received prophylactic teicoplanin. This was validated by dividing the total amount of drug issued to theatres during the study period (9923 g), by the average dose prescribed (528 mg), giving 18 794 patients.

Calculating the rate of IgE-mediated teicoplanin anaphylaxis

The lower end of the range included nine probable and definite cases divided by the higher estimate for the number of patients exposed to teicoplanin (18 794 patients). The upper end included the nine probable cases, definite cases and the two uncertain cases, divided by the lower estimate for the number of patients exposed to teicoplanin (18 200 patients).

We calculated the rate of IgE-mediated anaphylaxis to teicoplanin to be between 0.048% and 0.060% (equating to between 1:2088 and 1:1655).

Calculating the rate of IgE-mediated teicoplanin anaphylaxis in the 12 months before and after the issuing of guidance to administer teicoplanin as an intravenous infusion over 30 min

To establish whether advising all staff administering teicoplanin to dilute the drug in 100 ml of 0.9% sodium chloride and infuse over 30 min had any effect on the rate of teicoplanin anaphylaxis, we compared 12 months before and 12 months after the guidance changed (see Table 6).

In the 12 months before, we estimated that between 7242 and 7245 patients received prophylactic teicoplanin. Eight cases of suspected anaphylaxis attributed to the administration of teicoplanin: four were categorised as definite IgE-mediated anaphylaxis, three as probable and one was excluded. Using the methods described above, we calculated the rate of IgE-mediated anaphylaxis to teicoplanin during this period to be 0.097% (equating to 1:1035).

In the 12 months after the recommendation, we estimated that between 7317 and 8390 patients received teicoplanin. Six cases of suspected anaphylaxis were attributed to the administration of teicoplanin: one was categorised as definite IgE-mediated anaphylaxis, one as probable, two uncertain and two were excluded. Using the method described above, we calculated the rate of IgE-mediated anaphylaxis to teicoplanin during this period to be between 0.021% and 0.055% (equating to between 1:4195 and 1:1829).

Discussion

Within one month of the first reaction, the DTC prospectively encouraged the reporting and investigation of all suspected cases. Due to the nature of the institution and the

Table 4

Administration characteristics

Patient	Date of procedure	Previous documented teicoplanin	Planned dose	Rate of administration	Other drugs received
1	20/11/2013	Yes	474 mg given (950 mg total)	2nd Bolus. 4 aliquots in 5 min documented. Total 20 ml volume. 1st bolus of 237 mg, 2mins later 2nd bolus of 237 mg, then stopped	**midazolam**, fentanyl, propofol, remifentanyl, rocuronium, gentamicin
2	15/01/2014	Unknown	800 mg	Not stated only 'IV stat'	rocuronium, gentamicin
3	14/01/2014	Unknown	800 mg	IV bolus over 2 min	fentanyl, propofol, **lidocaine**, **ketamine**, gentamicin, **paracetamol**, **morphine**
4	25/04/2014	Yes	200 mg	Not stated	fentanyl, propofol, **ondansetron**
5	17/07/2014	Yes	200 mg	Only 'slow IV' stated	fentanyl, propofol, rocuronium, midazolam, **levobupivacaine**
6	24/07/2014	Yes	400 mg	Bolus 5–10 min	remifentanyl, propofol, midazolam, gentamicin
7	27/08/2014	Yes	600 mg	Not stated	midazolam, fentanyl, propofol, ketamine, ondansetron
8	12/09/2014	Unknown	800 mg total dose (in 6 ml, less than 1 ml given (i.e. <133 mg)	Slow IV bolus	**bupivacaine**, fentanyl
9	17/11/2014	Yes	800 mg	Infusion over 30 mins	propofol, remifentanyl, rocuronium, gentamicin
10	06/03/2015	Unknown	400 mg	Small amounts over time	fentanyl, propofol
11	24/03/2015	Yes	600 mg	Slow IV bolus	fentanyl, rocuronium, propofol
12	09/07/2015	Yes	600 mg	IV infusion over 30 min	fentanyl, propofol, levobupivacaine, ondansetron
13	09/09/2015	Unknown	400 mg	IV infusion over 30 min	fentanyl, rocuronium, propofol, ketamine
14	16/10/2015	Unknown	800 mg	IV infusion over 30 min	fentanyl, rocuronium, propofol

very high levels of concern relating to these cases, we are confident that no cases were missed during the study period: each case reached the authors' attention via the incident reporting system and regular updates from our lead anaesthetist.

Our cases occurred across a wide range of ages (13–61 years) and operations reflecting our institution's population; however, there was a notable female preponderance (10:4) in the suspected cases. This was unexpected and may be explained by the relatively small numbers involved. The most common clinical features were a widespread rash and circulatory compromise, particularly hypotension. These symptoms were consistent with anaphylaxis. In contrast, it was notable that bronchospasm occurred in comparatively few cases. Six of the nine definite/probable cases had a prior history of administration documented. This is typical of anaphylaxis, where previous safe administration does not guarantee that re-exposure to the same drug will remain uneventful.

There were concerns that cases of suspected anaphylaxis to teicoplanin may have been due to rate-related administration reactions, which are known to occur with other glycopeptide-related antimicrobials [3]. In October 2014, the DTC advised all staff administering teicoplanin to dilute the drug in 100 ml of 0.9% sodium chloride and infuse over 30 min instead of the manufacturer's recommendation of slow bolus injection. This advice was given to see whether slowing the rate of administration would reduce the number of reported cases of suspected anaphylaxis. Although the rate of IgE-mediated anaphylaxis to teicoplanin in the 12 months before the recommendation (0.097%) was higher than in the 12 months after (0.021%–0.055%), the numbers are too small to determine whether infusion-related reactions (not anaphylaxis) could account for this difference.

Classification of the suspected cases highlighted anomalies with using MCT and skin testing as supportive diagnostic tests. Our study shows that MCT, a product of mast cell degranulation, is raised in many but not all cases of IgE-mediated anaphylaxis to teicoplanin: a raised MCT was seen in seven of the nine probable/definite cases, and in both the excluded cases where anaphylaxis was attributed to a co-administered agent by SPT (Patient 5 to rocuronium and Patient 12 to chlorhexidine). In the two probable/definite cases which did not have an MCT rise (Patients 2 and 7), a

Table 5

Features of suspected teicoplanin reactions as categorised by Savic *et al.* [6]

Case number	Onset <15 min	≥2 clinical features	Positive MCT increase[a]	MCT values (micrograms l^{-1})	Positive skin testing/re challenge to coadministered agents	Positive skin testing/re challenge to teicoplanin	Category according to Savic *et al.*'s criteria
1	✓	✓	✓	200, 81.8, 183, 12.2	✗	✓	Definite
2	✓	✓	✗	6.1, 2.8, 6.4	✗	✓	Probable
3	✓	✓	✓	3.6, 14.7, 14.8	✗	✗	Probable
4	✓	✓	✓	42.2	✗	✓	Definite
5	✓	✓	✓	98.4, 74.3, 4.7	✓ (rocuronium)	✗	Excluded
6	✓	✓	✓	14.6, 12.4, 3.4	✗	✓	Definite
7	✓	✓	✗	1.5, 1.6	✗	✓	Probable
8	✓	✓	✓	53, 69.4, 3.4	✗	✓	Definite
9	✓	✓	✓	35.9, 24.7	✗	✗	Probable
10	✗	-	-	Not tested	Not tested	Not tested	Excluded
11	✓	✓	-	Not tested	✗	✓	Definite
12	✗	✓	✓	4.8, 19.6	✓ (chlorhexidine)	✗	Excluded
13	✓	✓	✗	2.6, 6.2, 7.8	✗	✗	Uncertain
14	✓	✓	✗	1.0, 1.3, 1.1	✗	✗	Uncertain

[a]Reference range for normal mast cell tryptase (MCT) is 2–11.4 micrograms l^{-1}

Table 6

Calculation of the rate of IgE-mediated anaphylaxis to teicoplanin in the 12 months before and after issuing the DTC recommendation

	Issuing of guidance to administer teicoplanin as an IV infusion	
	Before	**After**
Number of definite and probable cases	7	2
Number of definite, probable and uncertain cases	7	4
Total number of procedures	9409	9503
Total amount of teicoplanin issued to theatres (g)	3824	4430
Method 1	7245	7317
Percentage of surgical procedures that received prophylactic teicoplanin	77%	77%
Method 2	7242	8390
Rate of IgE-mediated anaphylaxis to teicoplanin	0.097% (1:1035)	0.021–0.055% (1:4195 and 1:1829)

diagnosis was made based on a strong clinical history and SPT alone. Discrepancies may occur as measurement is time-sensitive. Additionally, Laroche and colleagues have described anaphylaxis caused by an immunological pathway not involving tryptase release from mast cells, which may explain these discrepancies [9].

One patient (Patient 13) had a peak in MCT levels which remained within the reference range, and so was categorised as uncertain instead of probable according to Savic *et al.*'s criteria. The significance of this peak in MCT levels is unclear, but would have increased the overall rate of teicoplanin anaphylaxis had it been considered positive.

Two of the probable cases (Patients 2 and 9) appeared to have anaphylaxis to teicoplanin, but had negative SPT. Both were immediate severe reactions, with MCT rises, and negative SPT to all other coadministered agents. These may be false negative results due to suboptimal concentrations of teicoplanin being used during the skin-testing process.

Currently there is no standardised range of concentrations to be used for skin testing teicoplanin, and therefore negative SPT results should be treated with caution.

These anomalies highlight some of the limitations of using MCT and SPT alone as diagnostic tests for teicoplanin anaphylaxis. The likelihood of teicoplanin-induced anaphylaxis was assessed using published criteria incorporating clinical features in addition to MCT measurements and SPT. In view of these findings, we would recommend that a clinical diagnosis of anaphylaxis should be based on a strong history, even without a raised MCT or SPT. This is important in clinical practice, where skin testing is not immediately available.

The number of patients who received teicoplanin during the study period had to be estimated by dividing the amount of teicoplanin issued by the average dose prescribed. This value was similar to that calculated by a different method, using recent surgical prophylaxis audit data to estimate the number of surgical procedures that would have involved prophylactic teicoplanin.

Our study calculates the rate of IgE-mediated anaphylaxis to teicoplanin to be between 0.048% and 0.060% (equating to between 1:2088 and 1:1655) depending on whether probable and uncertain cases are included. As two methods were used to estimate the number of patients exposed, both were used to calculate the lower and upper limits of the range. Our observed rate of IgE-mediated anaphylaxis appears to be lower than that reported by the manufacturer (0.1–1%), but similar to published rates for other antimicrobials such as cephalosporins and penicillins (0.01–0.05%) [10–12]. Contact with several other NHS hospitals suggests that anaphylaxis to teicoplanin is not perceived to be a widespread problem, probably due to the under-reporting of suspected cases.

We did not receive any reports of teicoplanin anaphylaxis in clinical areas other than theatres. We felt this was possibly because most patients who receive teicoplanin at the RNOH, do so as a single dose at induction and no further doses postoperatively; however, there may be other reasons relating to the speed of infusion or concurrent administration of other drugs that warrants further investigation.

Conclusions

This is the first study to calculate a rate of IgE-mediated anaphylaxis to teicoplanin and is estimated to be between 0.048% and 0.060% (equating to between 1:2088 and 1:1655). Classification of the likelihood of anaphylaxis should be done according to standardised criteria. As with other allergies, MCT and SPT alone may be unreliable in the diagnosis of IgE-mediated teicoplanin anaphylaxis, and the clinical severity of reaction following administration should be used.

Competing Interests

There are no competing interests to declare.

We would like to acknowledge the anaesthetists working at the RNOH who reported cases of suspected anaphylaxis and made timely referrals to specialist allergy centres.

Contributors

All authors were involved in the design planning and conduct of the study. T.A. was responsible for writing the paper, and all the authors revised and approved the final version.

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